

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of

Confirmation No. 4003

HELLINGA et al.

Atty. Ref.: 1579-863

Serial No. 10/686,529

T.C./Art Unit: 1645

Filed: October 16, 2003

Examiner: R.A. Zeman

FOR: BIOSENSOR

\* \* \*

**APPEAL BRIEF UNDER 37 CFR § 41.37**

September 25, 2011

**Mail Stop Appeal Brief – Patents**

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

Appellants submit this Brief to appeal the Examiner's final rejections as set forth in his Office Action mailed September 14, 2011 (the "final Office Action"). The fee required under 37 CFR § 41.20(b)(2) is submitted herewith.

Since the Notice of Appeal is being filed concurrently, the Brief was initially due on November 14, 2011. Therefore, this Brief is timely filed.

Reversal of the Examiner's rejections of claims 1-2, 7-15, 31-32 and 38-40 by the Board of Patent Appeals and Interferences (the "Board") is respectfully requested.

**I. REAL PARTY IN INTEREST**

The assignee, Duke University, is the owner of all rights in this application, as well as the invention disclosed and claimed therein, by the assignment recorded on

December 11, 2003 in the Patent and Trademark Office (PTO) starting at reel 014780 and frame 0642.

## **II. RELATED APPEALS AND INTERFERENCES**

Appellants appealed the final rejections in the divisional application, Serial No. 11/785,591, which is related to, directly affects or is directly affected by, or has a bearing on the Board's decision in this appeal.

## **III. STATUS OF CLAIMS**

Claims 1-2, 7-15, 31-32 and 38-40 stand rejected, and are at issue in this appeal. They are listed in the Claims Appendix.

Claims 3-6, 16-30 and 33-37 were canceled without prejudice or disclaimer.

## **IV. STATUS OF AMENDMENTS**

No amendment was filed subsequent to the final Office Action.

## **V. SUMMARY OF CLAIMED SUBJECT MATTER**

The invention of the appealed claims are directed to biosensor for glucose, which comprises a glucose binding protein (GBP) and at least one reporter group attached at one or more positions 10, 93 and/or 183 of the GBP's amino acid sequence, wherein binding of glucose in a glucose-binding pocket of the biosensor causes a change in signaling by the reporter group.

Independent claim 1 is directed to biosensors for glucose, which comprise a glucose binding protein (GBP) and at least one reporter group attached at position 183 of the GBP's amino acid sequence, wherein binding of glucose in a glucose-binding pocket of the biosensor causes a change in signaling by the reporter group. Support for the claim is found, inter alia, at: page 2, line 28, to page 3, line 15, of the specification is a summary of the claimed biosensors; page 9, line 13, of the specification teaches that glucose is a ligand of GBP; and page 58, lines 2-8, of the specification (i.e., original claim 1).

Dependent claim 2 requires that the glucose binding protein is a W183C mutant. Support for the claim is found, inter alia, at page 13, lines 16-17, of the specification (i.e., "said GBP is a W183C mutant" of claims 27 and 33); line 31 of Table 3 on page 22 of the specification; line 1 in Table 5 on page 35 of the specification; and page 55, lines 11-20, of the specification.

Dependent claims 11-12 require a standard intensity change ( $\Delta I_{\text{std}}$ ) greater than 0.25 or 0.9 of the biosensor upon binding of glucose. They are supported, inter alia, by page 59, lines 11-14, of the specification (i.e., original claims 11-12).

Dependent claims 13-14 require a maximum value of the standard ratiometric change ( $\Delta R_{\text{max}}$ ) greater than 1.25 or 2.5 of the biosensor upon binding of glucose. They are supported, inter alia, by page 59, lines 16-19, of the specification (i.e., original claims 13-14).

Dependent claim 31 requires that the reporter group is acrylodan. Support for the claim is found, inter alia, at page 4, line 14, of the specification and page 15, lines 18-19, of the specification.

Independent claim 15 is directed to biosensors for glucose, which comprise a glucose binding protein (GBP) and at least one reporter group attached at one or more of positions 10, 93 and/or 183 of the GBP's amino acid sequence, wherein binding of glucose in a glucose-binding pocket of the biosensor causes a change in signaling by the reporter group. Support for the claim is found, inter alia, at: page 2, line 28, to page 3, line 15, of the specification is a summary of the claimed biosensors; page 9, line 13, of the specification teaches that glucose is a ligand of GBP; and page 58, lines 2-8, of the specification (i.e., original claim 1).

Independent claim 32 is directed to a biosensor for glucose, which comprises a glucose binding protein (GBP) and acrylodan covalently attached at position 183 of the GBP's amino acid sequence, wherein binding of glucose in a glucose-binding pocket of the biosensor causes a change in signaling by the reporter group. Support for the claim is found, inter alia, at: page 2, line 28, to page 3, line 15, of the specification is a summary of the claimed biosensors; page 9, line 13, of the specification teaches that glucose is a ligand of GBP; page 13, line 17, of the specification teaches that acrylodan is covalently attached; and page 58, lines 2-8, of the specification (i.e., original claim 1).

Therefore, the invention as presently claimed is clearly supported by Appellants' disclosure as originally filed.

## **VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL**

On ground of nonstatutory obviousness-type double patenting, was it proper to reject claims 1-2, 7-15, 31-32 and 38-40 as allegedly unpatentable over claims 1-8 of Patent No. 6,277,627?

Under 35 U.S.C. 112, 1st paragraph, was it proper to reject claims 1-2, 7-14 and 31-32 as allegedly failing to comply with the written description requirement?

Under 35 U.S.C. 112, 2nd paragraph, was it proper to reject claims 1-2, 7-15 and 31-32 as allegedly indefinite?

Under 35 U.S.C. 103(a), was it proper to reject claims 1-2, 7-15, 31-32 and 38-40 as allegedly unpatentable over Hellinga (WO 99/34212)?

Under 35 U.S.C. 103(a), was it proper to reject claims 1-2, 7-15, 31-32 and 38-40 as allegedly unpatentable over Hellinga (US 6,277,627)?

Under 35 U.S.C. 103(a), was it proper to reject claims 1-2, 7-15 and 38-40 as allegedly unpatentable over Amiss et al. (US 2003/0134346)?

Under 35 U.S.C. 103(a), was it proper to reject claims 1-2, 7-15 and 38-40 as allegedly unpatentable over Amiss et al. (US 6,855,556)?

## **VII. ARGUMENTS**

Claims 1-2, 7-15, 31-32 and 38-40 do not stand or fall together. Claims 1-2, 7-15 and 31-32 were rejected under Section 112, first and second paragraphs. Claims 1-2, 7-15, 31-32 and 38-40 were rejected for double patenting. Claims 31-32 were rejected as obvious over Hellinga (either WO 99/34212 or US 6,277,627) but not Amiss (either US 2003/0134346 or US 6,855,556).

First, if the Board sustains the Section 112 rejections and reverses the prior art rejections are reversed, claims 38-40 would be allowable after reformatting in independent form. Even if the Board also sustains the double patenting rejection, submission of a terminal disclaimer would make claims 38-40 allowable in this situation.

Second, claims 31-32 are directed to a specific embodiment of the invention in which the reporter group is acrylodan. They are argued separately because they require different combinations of limitations that should be compared separately against the prior art (n.b. Section 103 rejections in view of Hellinga only).

Third, claims 11-14 are directed to a specific embodiment of the invention in which, upon biosensor binding glucose, the standard intensity change is greater than 0.25 or 0.9 (claims 11-12) or standard ratiometric change is greater than 1.25 or 2.5 (claims 13-14). They are argued separately because they require different combinations of limitations that should be compared separately against the prior art when the Section 112 rejections are reversed (n.b. Section 103 rejections in view of Hellinga and Amiss).

These issues are separately argued below and demonstrate that there are independent bases for patentability. Therefore, Appellants' claims should be considered in four groups: (i) claims 1-2, 7-10 and 15 (allowance of these claims should make the other claims allowable); (ii) claims 11-14; (iii) claims 31-32; and (iv) claims 38-40.

### *Double Patenting*

Claims 1-2, 7-15, 31-32 and 38-40 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-8 of Patent No. 6,277,627. Appellants traverse because their claimed invention is not prima facie obvious as compared to the claims of the '627 patent. Furthermore, even if prima facie obvious, the presently claimed invention has properties that are unexpected by the prior art and the claims of the '627 patent.

Initially, it is noted that the Examiner's Section 112 rejections contradict the PTO's previous determination that the claims of the '627 patent, which also refer to a position in the GBP's amino acid sequence, satisfy all requirements for patentability.

Appellants' claims are directed using of a glucose binding protein (GBP) having at least one reporter group attached at one or more of position(s) 10, 93 and/or 183 of GBP's amino acid sequence. By contrast, claims 1-8 of the '627 patent only mention position 255 where a reporter group is attached to GBP.

Claims 1-2, 7-15, 31-32 and 38-40

Appellants' claims require that at least one reporter group is attached at one or more of position(s) 10, 93 and/or 183 of GBP's amino acid sequence. One of ordinary skill in the art would not have found this to be an obvious difference between Appellants' claimed invention and claims 1-8 of the '627 patent. The Examiner failed to specifically address how one of ordinary skill in the art would have selected positions 10, 93 and 183 of GBP's amino acid sequence for attachment of at least one reporter group with a reasonable expectation of success. The Examiner cannot depend on the Marvin et al. reference in a double patenting rejection because only claims 1-8 of the '627 patent were cited in this rejection.

Here, assuming for the sake of argument that the '627 patent contemplated attachment at any position within the GBP, the Examiner failed to identify a reason to select position 183 for attachment as required by Appellants' claims, especially in light of the unexpected results discussed below. Further, the Examiner provided no evidence that there was a reasonable expectation of success to attach a reporter group at any position within GBP such that "binding of glucose in a glucose-binding pocket of said

biosensor causes a change in signaling by said reporter group” as required by Appellants’ claims. Therefore, on both grounds, a prima facie case of obviousness was not established because it would not have been obvious from claims 1-8 of the ‘627 patent to make the biosensor of Appellants’ claimed invention.

It was alleged by the Examiner that “[claims 1-8 of the ‘627 patent] encompass all possible attachment positions within the GBP and the disclosure of the cited patent contemplates the same.” His reliance on the specification of the ‘627 patent to support a double patenting rejection is improper because only claims 1-8 of the ‘627 patent were cited in this rejection. The Examiner also failed to explain why the present claims 27-28 and 33-34, which are directed to a W183C mutant of GBP and also encompassed by claim 4 of the ‘627 patent, were not rejected for obviousness-type double patenting when he rejected that the present claims 17-18 on that ground. An obviousness determination cannot be made when the limitation “a biosensor which comprises a glucose binding protein (GBP) and at least one reporter group attached at position 183 of said GBP” is disregarded. In determining prima facie obviousness, all limitations of the claims must be considered and given weight. See *Ex parte Grasselli*, 231 USPQ 393 (BPAI 1983).

Since this rejection is substantially the same as the obviousness rejections over Hellinga (WO 99/34212 or US 6,277,627), withdrawal of those obviousness rejection should require withdrawal of this obviousness-type double patenting rejection too.

#### Claims 11-14

Appellants’ claims 11-12 require a standard intensity change ( $\Delta I_{\text{std}}$ ) greater than 0.25 or 0.9, respectively, of the biosensor upon binding of ligand. The Examiner did not



explain why one of ordinary skill in the art would have found it obvious to modify claims 1-8 of the '627 patent with a reasonable expectation of success to satisfy the requirements of the present claims 11-12. Therefore, the Examiner has not established a prima facie case of obviousness.

Appellants' claims 13-14 require a maximum value of the standard ratiometric change ( $\Delta R_{\max}$ ) greater than 1.25 or 2.5, respectively, of the biosensor upon binding of ligand. The Examiner did not explain why one of ordinary skill in the art would have found it obvious to modify claims 1-8 of the '627 patent to satisfy the requirements of the present claims 13-14. Therefore, the Examiner has not established a prima facie case of obviousness.

For these separate reasons, this rejection should be reversed with respect to claims 11-14 even if the obviousness-type double patenting rejection of claims 1-2, 7-10, 15, 31-32 and 38-40 is sustained.

#### Claims 31-32

Appellants' claims 31-32 require that the reporter group is acrylodan. The Examiner did not explain why one of ordinary skill in the art would have found it obvious to modify claims 1-8 of the '627 patent with a reasonable expectation of success to satisfy the requirement of the present claims 11-12. Therefore, the Examiner has not established a prima facie case of obviousness.

For this separate reason, this rejection should be reversed with respect to claims 31-32 even if the obviousness-type double patenting rejection of claims 1-2, 7-15 and 38-40 is sustained.

Appellants urge the Board to reverse the double patenting rejection.

*35 U.S.C. 112 – Written Description*

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 1-2, 7-14 and 31-32 were rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. Appellants traverse because their specification teaches a representative number of species (i.e., amino acid sequences of different glucose binding proteins and examples of biosensors) within the claimed genus. The guidance that the Examiner alleges would be required but is absent from this specification would have been known to a person skilled in the art at the time this application was filed.

Appellants submit that this rejection contradicts the PTO's previous determination that the claims of Patent No. 6,277,627 patent satisfy all requirements for patentability. The '627 patent contains: claim 1 ("A glucose biosensor comprising a glucose binding protein (GBP) and a reporter group that transduces a detectable signal, wherein said reporter group is attached to said GBP so that a signal transduced by said reporter group when said GBP is bound to glucose differs from a signal transduced by said reporter group when said GBP is not bound to glucose"); claim 12 ("wherein alanines are present at positions 154 and 183"); and claim 14 ("wherein said reporter group is

attached to a cysteine residue at position 255”) that refer to specific positions in the GBP’s amino acid sequence. Since the ‘627 patent is incorporated by reference in the present specification, the latter also satisfies the written description requirement.

The requirements of Section 112 are satisfied by the present specification and claims without providing a “baseline sequence” for GBP as the Examiner alleged is required to satisfy those requirements. Patent No. 6,277,627 is cited for describing *E. coli* periplasmic binding proteins, including the amino acid sequence of glucose binding protein (GBP), on page 2, lines 3-6, of the present specification. Its contents are also incorporated by reference at page 57, lines 11-14, of the present specification.

The sequences of GBP from bacteria other than *E. coli* were also known in the prior art. For example, GBP were cloned from *Pseudomonas* spp. (Cuskey et al., 1985, *Journal of Bacteriology*, 162:865-871) and archae *Sulfolobus solfataricus* (Albers et al., 1999, *Journal of Bacteriology*, 181:4285-4291). One of skill in the art would be able to align different GBP and identify a position corresponding to positions 10, 93 and 183 of the *E. coli* GBP as taught in the prior art (Tam & Saier, 1993, *Microbiological Reviews*, 57:320-346). A specification need not teach, and preferably omits, what is well known in the art. See *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

Therefore, for the above reasons, one of skill in the art would understand that Appellants’ specification as well as general knowledge (i.e., what is well known in the prior art) satisfy the written description requirement for the present claims.

Appellants urge the Board to reverse the written description rejection because the specification conveys to a person skilled in the art that they were in possession of the claimed invention.

*35 U.S.C. 112 – Definiteness*

Claims 1-2, 7-15 and 31-32 were rejected under Section 112, second paragraph, as allegedly indefinite. Appellants traverse because the proper test for definiteness is whether “those skilled in the art would understand what is claimed when the claim is read in light of the specification” (emphasis added). *Orthokinetics v. Safety Travel Chairs*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986).

M.P.E.P. § 2173.02 requires the Examiner to read the claims in light of the specification. In Appellants’ claims, positions 10, 93 and 183 refer to the GBP’s amino acid sequence. U.S. Patent 6,277,627 is cited by Appellants at page 2, lines 3-6, and page 57, lines 11-14, of their specification as describing *E. coli* periplasmic binding proteins and the amino acid sequence of GBP, respectively. The contents of the ‘627 patent are incorporated by reference on page 57, lines 11-14, of the present specification. A specification need not teach, and preferably omits, what is well known in the art. See *Hybri-tech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

No specific reference to a sequence identifier is required because the GBP’s are known in the art. The numbering of residues within the amino acid sequence is well known in the art and would be understood by those skilled in the art. For example, the amino acid sequence was not required for the Examiner to thoroughly search the prior art for the claimed subject matter because he knew the location of positions 10, 93 and 183 in the GBP’s amino acid sequence. Claims 12 and 14 of the ‘627 patent refer to positions 154, 183 and 255 in the amino acid sequence. Here, the same numbering of the amino acid sequence is used in Appellants’ specification and the ‘627 patent.

Therefore, for the above reasons, one of skill in the art would understand what Appellants are claiming when the present claims are read in light of their specification as required by *Orthokinetics*.

Appellants urge the Board to reverse this rejection because the present claims are clear and definite.

### *35 U.S.C. 103 – Nonobviousness*

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR Int'l v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See *id.* (“Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue”). The use of hindsight reasoning is impermissible. See *id.* at 1397 (“A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning”). Thus, a *prima facie* case of obviousness requires “some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct.” *Kahn* at 1335; see *KSR* at 1396. An inquiry should be made as to “whether the improvement is more than the

predictable use of prior art elements according to their established functions.” Id. But a claim that is directed to a combination of prior art elements “is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-2, 7-15, 31-32 and 38-40 were rejected under Section 103(a) as allegedly unpatentable over Hellinga (WO 99/34212). Appellants traverse because the differences between their claimed invention and Hellinga ‘212 would not have been obvious to one of ordinary skill in the art with a reasonable expectation of success.

Appellants’ claims require a glucose binding protein (GBP) having at least one reporter group at one or more of position(s) 10, 93 and/or 183. See Table 5 at page 35 of the present specification. But Hellinga ‘212 fails to teach or make obvious this specific position within a GBP for attaching a reporter group. Moreover, there was no technical or legal rationale provided by the Examiner for why one of ordinary skill in the art would have attached a reporter group at position 10, 93 or 183 in a GBP with a reasonable expectation of success. Instead, it was alleged that “the skilled artisan [would] utilize any or all of the possible binding sites” by the Examiner. This was not an acceptable reason to support a finding of prima facie obviousness because it merely invites one of ordinary skill in the art to experiment by attaching a reporter group at “any or all” positions of the amino acid sequence of GBP. Thus, the Examiner’s finding of obviousness clearly relied on hindsight.

Moreover, the Examiner also provided no evidence that there was a reasonable expectation of success to attach a reporter group at “any or all” positions within GBP

such that “binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group” as required by Appellants’ claims.

Claims 1-2, 7-15, 31-32 and 38-40

Lacking both an acceptable reason for attaching a reporter group at position 183 within GBP and a reasonable expectation of success that such proteins would be suitable for including in biosensors, a prima facie case of obviousness was not established by the Examiner. Otherwise, he was required to consider Appellants’ claimed invention has (1) decreased binding affinity for glucose and (2) increased fluorescence characteristics and inquire “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *KSR* at 1396.

Claims 11-14

The Examiner did not take into account the properties of a biosensor obtained by attaching a reporter group at position 183.  $\Delta I_{\text{std}}$  and  $\Delta R_{\text{max}}$  properties of biosensors were experimentally determined by Appellants and disclosed in their specification. All claim limitations must be considered in determining the patentability of claims against the prior art. M.P.E.P. § 2143.03 and *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970). There was insufficient basis for the Examiner to find claims 11-14 to be obvious (cf. “the biosensor with a reporter group at position 183, which is encompassed by Hellinga in light of *KSR*, would necessarily have the same biochemical properties as that of the instant invention” emphasis added) when he contradicted himself by maintaining that the prior art biosensor and the present invention are not identical (“Hellinga does not explicitly disclose the attachment of the reporter group(s) at positions 10, 93 or 183”). Here too, dependent claims 11-14 further limit the subject matter of independent claim 1. Accordingly,

biosensors within the scope of Appellants' claim 1 cannot all satisfy the requirements of dependent claims 11-14. Therefore, the Examiner's allegation was factually incorrect: the biosensors of Appellants' claims do not necessarily have the same biochemical properties.

#### Claims 31-32

Appellants' claimed invention is patentable even if prima facie obvious because attaching at least one reporter group (e.g., acrylodan) at position 183 of GBP provides the unexpected and surprising properties of (1) decreased binding affinity for glucose and (2) increased fluorescence characteristics. For a diabetic patient, a biosensor tuned to physiological concentrations of glucose in the millimolar range is a clear advantage, which is taught by Appellants at page 53, lines 11-20, of their specification. Decreased binding affinity is achieved by attaching a reporter group at position 183 of GBP. See page 35 of the present specification. In Table 5, it can also be seen that the fluorescence characteristics  $\Delta I_{\text{std}}$  and  $\Delta R_{\text{max}}$  are desirable for a biosensor of glucose. Fig. 5A shows that the fluorescence response to log concentrations of glucose is linear. By ratiometry, clinically relevant ranges of glucose may be measured and different clinical states easily distinguished as shown in Fig. 8A.

For these reasons, Appellants' claims are patentable over Hellinga '212.

Claims 1-2, 7-15, 31-32 and 38-40 were rejected under Section 103(a) as allegedly unpatentable over Hellinga (US 6,277,627). Appellants traverse because the differences between their claimed invention and Hellinga '627 would not have been obvious to one of ordinary skill in the art with a reasonable expectation of success.



Appellants' claims require a glucose binding protein (GBP) having at least one reporter group at one or more of position(s) 10, 93 and/or 183. See Table 5 at page 35 of the present specification. But Hellinga '627 fails to teach or make obvious this specific position within a GBP for attaching a reporter group. Moreover, there was no technical or legal rationale provided by the Examiner for why one of ordinary skill in the art would have attached a reporter group at position 10, 93 or 183 in a GBP with a reasonable expectation of success. Instead, it was alleged that "the skilled artisan [would] utilize any or all of the possible binding sites" by the Examiner. This was not an acceptable reason to support a finding of prima facie obviousness because it merely invites one of ordinary skill in the art to experiment by attaching a reporter group at "any or all" positions of the amino acid sequence of GBP. Thus, the Examiner's finding of obviousness clearly relied on hindsight.

Moreover, the Examiner also provided no evidence that there was a reasonable expectation of success to attach a reporter group at "any or all" positions within GBP such that "binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group" as required by Appellants' claims.

Claims 1-2, 7-15, 31-32 and 38-40

Lacking both an acceptable reason for attaching a reporter group at position 183 within GBP and a reasonable expectation of success that such proteins would be suitable for including in biosensors, a prima facie case of obviousness was not established by the Examiner. Otherwise, he was required to consider Appellants' claimed invention has (1) decreased binding affinity for glucose and (2) increased fluorescence charac-

teristics and inquire “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *KSR* at 1396.

#### Claims 11-14

The Examiner did not take into account the properties of a biosensor obtained by attaching a reporter group at position 183.  $\Delta I_{\text{std}}$  and  $\Delta R_{\text{max}}$  properties of biosensors were experimentally determined by Appellants and disclosed in their specification. All claim limitations must be considered in determining the patentability of claims against the prior art. M.P.E.P. § 2143.03 and *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970). There was insufficient basis for the Examiner to find claims 11-14 to be obvious (cf. “the biosensor with a reporter group at position 183, which is encompassed by Hellinga in light of *KSR*, would necessarily have the same biochemical properties as that of the instant invention” emphasis added) when he contradicted himself by maintaining that the prior art biosensor and the present invention are not identical (“Hellinga does not explicitly disclose the attachment of the reporter group(s) at positions 10, 93 or 183”). Here too, dependent claims 11-14 further limit the subject matter of independent claim 1. Accordingly, biosensors within the scope of Appellants’ claim 1 cannot all satisfy the requirements of dependent claims 11-14. Therefore, the Examiner’s allegation was factually incorrect: the biosensors of Appellants’ claims do not necessarily have the same biochemical properties.

#### Claims 31-32

Appellants’ claimed invention is patentable even if *prima facie* obvious because attaching at least one reporter group (e.g., acrylodan) at position 183 of GBP provides the unexpected and surprising properties of (1) decreased binding affinity for glucose

and (2) increased fluorescence characteristics. For a diabetic patient, a biosensor tuned to physiological concentrations of glucose in the millimolar range is a clear advantage, which is taught by Appellants at page 53, lines 11-20, of their specification. Decreased binding affinity is achieved by attaching a reporter group at position 183 of GBP. See page 35 of the present specification. In Table 5, it can also be seen that the fluorescence characteristics  $\Delta I_{\text{std}}$  and  $\Delta R_{\text{max}}$  are desirable for a biosensor of glucose. Fig. 5A shows that the fluorescence response to log concentrations of glucose is linear. By ratiometry, clinically relevant ranges of glucose may be measured and different clinical states easily distinguished as shown in Fig. 8A.

For these reasons, Appellants' claims are patentable over Hellinga '627.

Claims 1-2, 7-15 and 38-40 were rejected under Section 103(a) as allegedly unpatentable over Amiss et al. (US 2003/0134346). Appellants traverse because the differences between their claimed invention and Amiss '346 would not have been obvious to one of ordinary skill in the art with a reasonable expectation of success.

Appellants' claims require a glucose binding protein (GBP) having at least one reporter group at one or more of position(s) 10, 93 and/or 183. See Table 5 at page 35 of the present specification. But Amiss '346 fails to teach or make obvious this specific position within a GBP for attaching a reporter group. Moreover, there was no technical or legal rationale provided by the Examiner for why one of ordinary skill in the art would have attached a reporter group at position 10, 93 or 183 in a GBP with a reasonable expectation of success. Instead, it was alleged that "the skilled artisan [would] utilize any or all of the possible binding sites" by the Examiner. This was not an acceptable reason to support a finding of prima facie obviousness because it merely invites one of

ordinary skill in the art to experiment by attaching a reporter group at “any or all” positions of the amino acid sequence of GBP. Thus, the Examiner’s finding of obviousness clearly relied on hindsight.

Moreover, the Examiner also provided no evidence that there was a reasonable expectation of success to attach a reporter group at “any or all” positions within GBP such that “binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group” as required by Appellants’ claims.

Claims 1-2, 7-15 and 38-40

Lacking both an acceptable reason for attaching a reporter group at position 183 within GBP and a reasonable expectation of success that such proteins would be suitable for including in biosensors, a prima facie case of obviousness was not established by the Examiner. Otherwise, he was required to consider Appellants’ claimed invention has (1) decreased binding affinity for glucose and (2) increased fluorescence characteristics and inquire “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *KSR* at 1396.

Appellants’ claimed invention is patentable even if prima facie obvious because attaching at least one reporter group (e.g., acrylodan) at position 183 of GBP provides the unexpected and surprising properties of (1) decreased binding affinity for glucose and (2) increased fluorescence characteristics. For a diabetic patient, a biosensor tuned to physiological concentrations of glucose in the millimolar range is a clear advantage, which is taught by Appellants at page 53, lines 11-20, of their specification. Decreased binding affinity is achieved by attaching a reporter group at position 183 of GBP. See page 35 of the present specification. In Table 5, it can also be seen that the fluores-

cence characteristics  $\Delta I_{\text{std}}$  and  $\Delta R_{\text{max}}$  are desirable for a biosensor of glucose. Fig. 5A shows that the fluorescence response to log concentrations of glucose is linear. By ratiometry, clinically relevant ranges of glucose may be measured and different clinical states easily distinguished as shown in Fig. 8A.

#### Claims 11-14

The Examiner did not take into account the properties of a biosensor obtained by attaching a reporter group at position 183.  $\Delta I_{\text{std}}$  and  $\Delta R_{\text{max}}$  properties of biosensors were experimentally determined by Appellants and disclosed in their specification. All claim limitations must be considered in determining the patentability of claims against the prior art. M.P.E.P. § 2143.03 and *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970). There was insufficient basis for the Examiner to find claims 11-14 to be obvious (cf. “the biosensor with a reporter group at position 183, which is encompassed by Amiss et al. in light of KSR, would necessarily have the same biochemical properties as that of the instant invention” emphasis added) when he contradicted himself by maintaining that the prior art biosensor and the present invention are not identical (i.e., this is an obviousness rejection under Section 103 instead of a Section 102 rejection). Here too, dependent claims 11-14 further limit the subject matter of independent claim 1. Accordingly, biosensors within the scope of Appellants’ claim 1 cannot all satisfy the requirements of dependent claims 11-14. Therefore, the Examiner’s allegation was factually incorrect: the biosensors of Appellants’ claims do not necessarily have the same biochemical properties.

For these reasons, Appellants’ claims are patentable over Amiss ‘346.

Claims 1-2, 7-15 and 38-40 were rejected under Section 103(a) as allegedly unpatentable over Amiss et al. (US 6,855,556). Appellants traverse because the differences between their claimed invention and Amiss '556 would not have been obvious to one of ordinary skill in the art with a reasonable expectation of success.

Appellants' claims require a glucose binding protein (GBP) having at least one reporter group at one or more of position(s) 10, 93 and/or 183. See Table 5 at page 35 of the present specification. But Amiss '556 fails to teach or make obvious this specific position within a GBP for attaching a reporter group. Moreover, there was no technical or legal rationale provided by the Examiner for why one of ordinary skill in the art would have attached a reporter group at position 10, 93 or 183 in a GBP with a reasonable expectation of success. Instead, it was alleged that "the skilled artisan [would] utilize any or all of the possible binding sites" by the Examiner. This was not an acceptable reason to support a finding of prima facie obviousness because it merely invites one of ordinary skill in the art to experiment by attaching a reporter group at "any or all" positions of the amino acid sequence of GBP. Thus, the Examiner's finding of obviousness clearly relied on hindsight.

Moreover, the Examiner also provided no evidence that there was a reasonable expectation of success to attach a reporter group at "any or all" positions within GBP such that "binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group" as required by Appellants' claims.

Claims 1-2, 7-15 and 38-40

Lacking both an acceptable reason for attaching a reporter group at position 183 within GBP and a reasonable expectation of success that such proteins would be suit-

able for including in biosensors, a prima facie case of obviousness was not established by the Examiner. Otherwise, he was required to consider Appellants' claimed invention has (1) decreased binding affinity for glucose and (2) increased fluorescence characteristics and inquire "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at 1396.

Appellants' claimed invention is patentable even if prima facie obvious because attaching at least one reporter group (e.g., acrylodan) at position 183 of GBP provides the unexpected and surprising properties of (1) decreased binding affinity for glucose and (2) increased fluorescence characteristics. For a diabetic patient, a biosensor tuned to physiological concentrations of glucose in the millimolar range is a clear advantage, which is taught by Appellants at page 53, lines 11-20, of their specification. Decreased binding affinity is achieved by attaching a reporter group at position 183 of GBP. See page 35 of the present specification. In Table 5, it can also be seen that the fluorescence characteristics  $\Delta I_{\text{std}}$  and  $\Delta R_{\text{max}}$  are desirable for a biosensor of glucose. Fig. 5A shows that the fluorescence response to log concentrations of glucose is linear. By ratiometry, clinically relevant ranges of glucose may be measured and different clinical states easily distinguished as shown in Fig. 8A.

#### Claims 11-14

The Examiner did not take into account the properties of a biosensor obtained by attaching a reporter group at position 183.  $\Delta I_{\text{std}}$  and  $\Delta R_{\text{max}}$  properties of biosensors were experimentally determined by Appellants and disclosed in their specification. All claim limitations must be considered in determining the patentability of claims against the prior art. M.P.E.P. § 2143.03 and *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970). There was

insufficient basis for the Examiner to find claims 11-14 to be obvious (cf. “the biosensor with a reporter group at position 183, which is encompassed by Amiss et al. in light of KSR, would necessarily have the same biochemical properties as that of the instant invention” emphasis added) when he contradicted himself by maintaining that the prior art biosensor and the present invention are not identical (i.e., this is an obviousness rejection under Section 103 instead of a Section 102 rejection). Here too, dependent claims 11-14 further limit the subject matter of independent claim 1. Accordingly, biosensors within the scope of Appellants’ claim 1 cannot all satisfy the requirements of dependent claims 11-14. Therefore, the Examiner’s allegation was factually incorrect: the biosensors of Appellants’ claims do not necessarily have the same biochemical properties.

For these reasons, Appellants’ claims are patentable over Amiss ‘556.

Appellants urge the Board to reverse the Section 103 rejections because their claimed invention would not have been obvious to one of ordinary skill in the art.



*Conclusion*

For the reasons discussed above, the Examiner's rejections are improper and they should be reversed by the Board. Appellants submit that the present claims are in condition for allowance and earnestly solicit an early Notice to that effect.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By:                     /Gary R. Tanigawa/                      
Gary R. Tanigawa  
Reg. No. 43,180

901 North Glebe Road, 11th Floor  
Arlington, VA 22203-1808  
Telephone: (703) 816-4000  
Facsimile: (703) 816-4100

## **VIII. CLAIMS APPENDIX**

1. (previously presented) A biosensor for glucose, which comprises a glucose binding protein (GBP) and at least one reporter group attached at position 183 of said GBP, wherein binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group.

2. (previously presented) The biosensor according to claim 1, wherein said GBP is a W183C mutant.

Claims 3-6 (canceled)

7. (previously presented) The biosensor according to claim 1, wherein said reporter group is covalently attached at position 183 of said GBP.

8. (previously presented) The biosensor according to claim 1, wherein said reporter group is noncovalently attached at position 183 of said GBP.

9. (original) The biosensor according to claim 1, wherein said reporter group is a redox cofactor.

10. (original) The biosensor according to claim 1, wherein said reporter group is a fluorophore.

11. (previously presented) The biosensor according to claim 1, wherein said biosensor's standard intensity change ( $\Delta I_{\text{std}}$ ) upon binding of glucose is greater than 0.25.

12. (original) The biosensor according to claim 11, wherein said  $\Delta I_{\text{std}}$  is greater than 0.9.

13. (previously presented) The biosensor according to claim 1, wherein said biosensor's maximum value of standard ratiometric change ( $\Delta R_{\text{max}}$ ) upon binding of glucose is greater than 1.25.

14. (original) The biosensor according to claim 13, wherein said  $\Delta R_{\text{max}}$  is greater than 2.5.

15. (previously presented) A biosensor for glucose, which comprises a glucose binding protein (GBP) and at least one reporter group attached at one or more amino acid positions of said GBP selected from the group consisting of 10, 93 and 183, wherein binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group.

Claims 16-30 (canceled)

31. (previously presented) The biosensor according to claim 2, wherein at least one reporter group is acrylodan.

32. (previously presented) A biosensor for glucose, which comprises a glucose binding protein (GBP) and acrylodan covalently attached at position 183 of said GBP, wherein binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group.

Claims 33-37 (canceled)

38. (previously presented) The biosensor according to claim 2, wherein said GBP is *E. coli* GBP.

39. (previously presented) The biosensor according to claim 15, wherein said GBP is *E. coli* GBP.

40. (previously presented) The biosensor according to claim 32, wherein said GBP is *E. coli* GBP.

**IX. EVIDENCE APPENDIX**

None.

**X. RELATED PROCEEDINGS APPENDIX**

None.